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Solid Phase Parallel Synthesis of Highly Substituted Thiophene Derivatives and Identification of Novel Phosphodiesterase-4 (PDE-4) Inhibitors

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Abstract: A versatile protocol for solid phase synthesis of highly substituted thiophene derivatives and their activity against the PDE-4 enzyme are discussed. This protocol employs 3-hydroxymethylthiophene-2-boronic acid (**5**) as the scaffold and sequential palladium catalyzed cross-coupling reactions as the C-C bond forming step. This methodology allows convenient modification of the thiophene core from three directions, giving rise to structurally diverse derivatives with overall high chemical purity and yield. A novel series of potent PDE-4 inhibitors have been identified from these compounds.

Introduction:

Cyclic nucleotide phosphodiesterases (PDEs) are members of a broad family of hydrolases responsible for the hydrolysis and consequent deactivation of the second messengers 3',5'-adenosine monophosphate (cAMP) and 3',5'-guanosine monophophate (cGMP). One of the these enzymes, PDE-4, has attracted considerable attention following its recognition as the primary enzyme responsible for the metabolism of cAMP in inflammatory and immune cells.[1,2] Potent and selective PDE-4 inhibitors are therefore attractive therapeutic agents for inflammation and immuno-modulation. Several selective PDE-4 inhibitors are currently being developed for treating depression [e.g., rolipram (**1**)], rheumatoid arthritis [e.g., piclamilast (**2**)] and asthma [e.g., ariflo (**3**)].[3] One of our efforts to identify novel PDE-4 inhibitors led to the identification of **4**,[4] a trisubstituted furan derivative. Despite its relatively weak activity against PDE-4[5] (IC_{50} 2.5μM) in comparison to existing classes of inhibitors, this compound has the appealing structural feature (2,5-diaryl substitution

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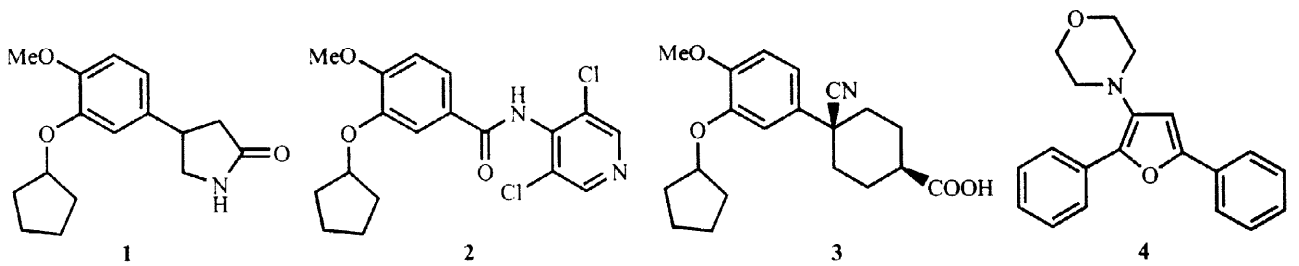
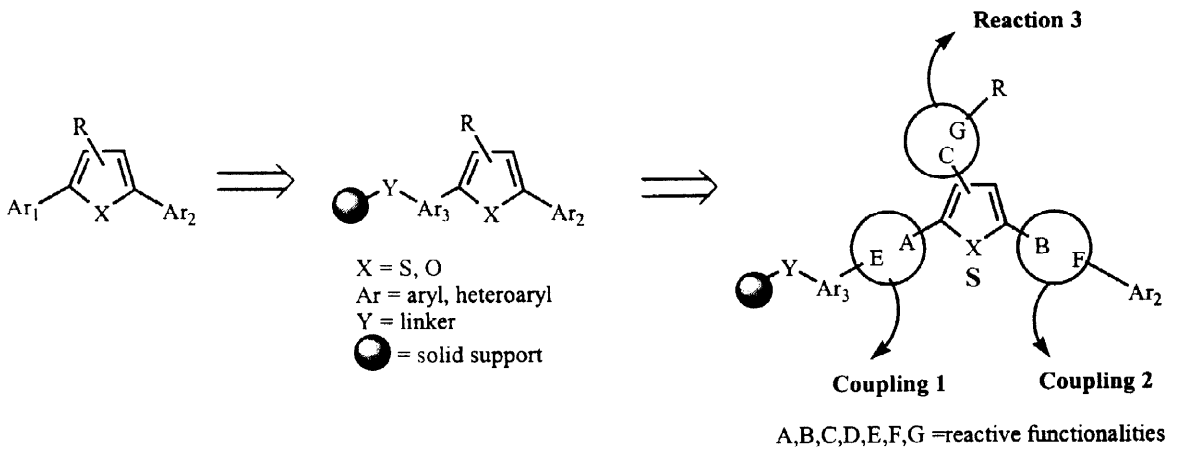
with a side chain at the 3-position) well suited for structure-activity relationship (SAR) exploration by employing combinatorial techniques.



Combinatorial synthesis of small organic molecules has evolved rapidly in the last few years to become a new paradigm for contemporary drug discovery.[6] While the recent emergence of various new techniques (e.g., solution phase combinatorial synthesis,[7] resin capturing and resin scavenging,[8] ion-exchange for acid-base extraction,[9] fluorous phase extraction[10] and synthesis on soluble polymers[11]) further enhances the practicality of combinatorial synthesis, solid phase chemistry continues to enjoy its dominant role partly due to the successful adaptation of many types of organic reactions onto solid supports.[12]



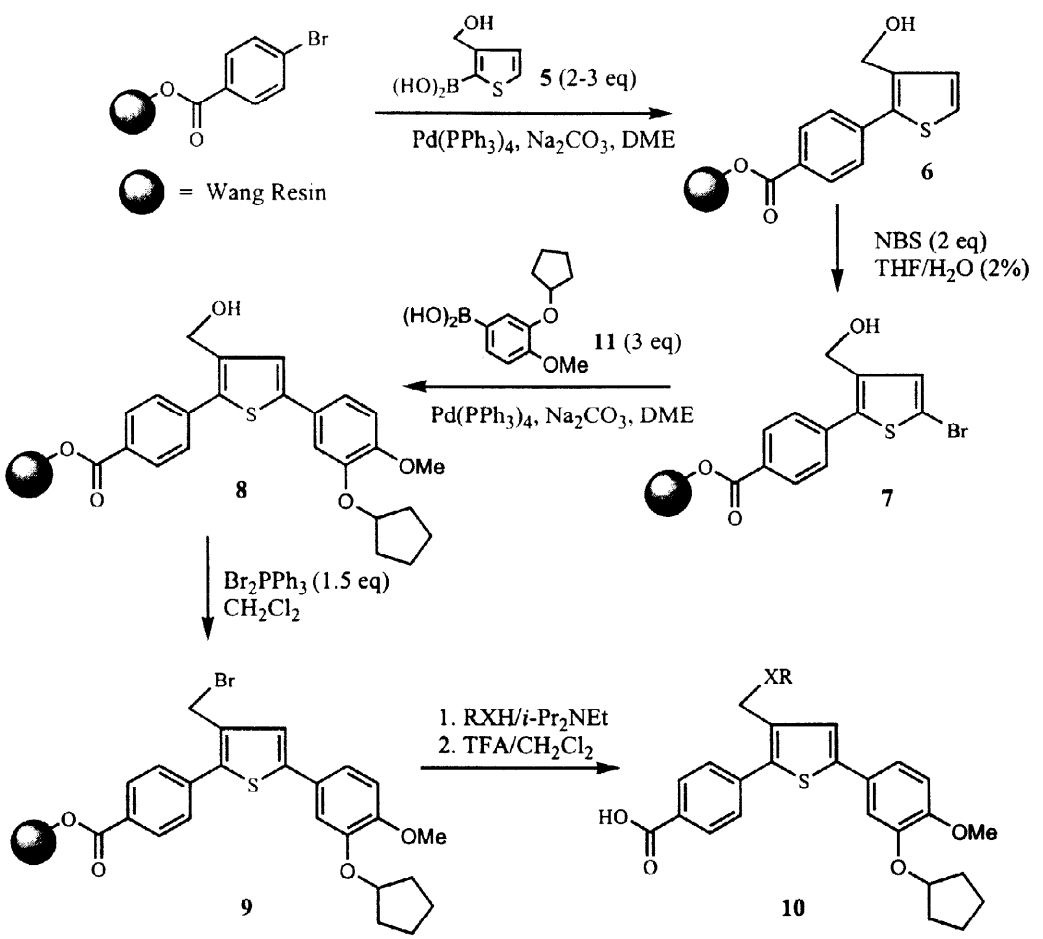
Scheme 1: Retro-synthetic analysis based on Scaffold **S**

A preliminary SAR investigation of biaryl analogs (both furan and thiophene derivatives) of structure **4** revealed that both aromatic rings were necessary for appreciable (high nM to μM) activity against the PDE-4 enzyme. It was also observed that the presence of a polar residue such as a carboxylic acid moiety on one of the aromatic rings was beneficial for both the solubility and activity of these compounds. Our efforts then focused on the development of general and versatile approaches for the preparation of thiophene or furan derivatives using a common scaffold such as **S** (**Scheme 1**), with particular emphasis on new carbon-carbon (C-C) bond formation. Furthermore, it is of general interest to explore versatile and mild methods for the

efficient construction of these small molecules on solid supports due to the lack of general literature examples.[13] In the present article, we will detail a divergent protocol for solid phase construction of single compound libraries of highly substituted thiophene derivatives containing either a carboxylic acid residue or a dimethylcarbinol moiety, and the identification of a novel series of PDE-4 inhibitors from them.[14]

Discussion

Our synthesis started with the identification of the multi-functional scaffold **S** suitable for our purposes. We were particularly interested in organometallic reagents such as boronic acids, zincates or stannanes since palladium catalyzed cross-coupling reactions of these reagents on solid supports were well established.[15] Among several candidates examined,[16] we discovered that 3-hydroxymethylthiophene-2-boronic acid (**5**)[17] served as an excellent candidate due to its high reactivity and easy accessibility. The solid phase synthetic sequence is illustrated in **Scheme 2**.



Scheme 2: Solid phase synthesis of thiophene analogs using boronic acid **5**

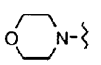
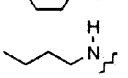
p-Bromobenzoate attached to Wang resin was reacted with boronic acid **5** under the standard aqueous conditions [$Pd(PPh_3)_4$ (3 mol%), Na_2CO_3 (aq), DME, 85-90 °C] to give intermediate **6**. A slight excess of boronic acid **5** to base (Na_2CO_3) was used to avoid hydrolysis of polymer-supported esters. Bromination of **6** was carried out in THF in the presence of approximately 2% (v/v) water using 2 equivalents of N-bromosuccinamide (NBS), yielding bromothiophene **7**. The addition of water was crucial for fast and selective bromination at room temperature.[18] The exact mechanism for the rate acceleration of water in the bromination process is not clear although it is known that polar solvents such as acetonitrile or DMF,[19] or the addition of acids[20] can have dramatic rate enhancement for bromination of electron rich aromatics with NBS.

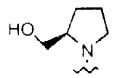
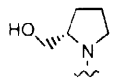
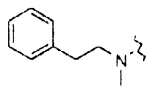
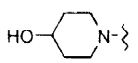
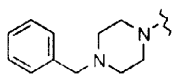
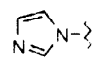
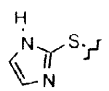
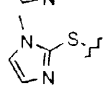
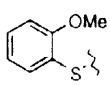
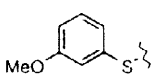
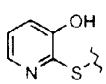
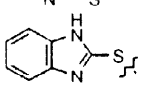
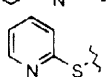
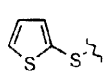
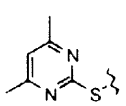
After the bromination process, it is important to wash the resin thoroughly with organic solvents such as THF or DMF and methanol until a colorless washing filtrate is achieved. This careful washing protocol ensures the complete removal of any excess NBS which is detrimental to the subsequent reaction (NBS attenuates the catalytic power of the palladium catalyst).

The bromide intermediate **7** was then reacted with boronic acid **11** under the aforementioned Suzuki coupling conditions to yield biarylthiophene intermediate **8**. The primary alcohol in **8** was converted to the corresponding bromide **9** with dibromotriphenylphosporane (Br_2PPh_3, 1.5 eq) in CH_2Cl_2. To examine the quality of the sequence before continuing with the production of single compound libraries, a portion of the resin (109 mg, 0.81 mmol/g theoretical loading) was treated with 5 eq of morpholine in DMF at room temperature for 1 hour and then cleaved with 20% trifluoroacetic acid (TFA) in CH_2Cl_2 for 30 min. This afforded 44 mg (84% yield) of the crude product **10a** as a yellow solid (TFA salt) with a purity of over 90% by both ^1H NMR and HPLC/MS analysis.

Encouraged by this finding, resin bound bromide **9** was reacted with a variety of amines and thiols and then cleaved with the same protocol, affording final products **10b-10t**. The purity of these compounds and their potency on inhibiting the PDE-4 mediated cAMP hydrolysis are summarized in **Table 1**.

Table 1: Summary of results of single compound library containing compounds **10**

Entry	Product	R	Purity[a]	Molecular Ion (M-1)	Yield (crude product)	IC_{50} (μM)
1	**10a**		92	492.5	84	>1
2	**10b**		~50[b]	---	---	--
3	**10c**		92	476.3	60	>1
4	**10d**		90	490.5	65	>1

5	**10e**		92	506.4	64	>1
6	**10f**		80	506.3	60	>1
7	**10g**		89	540.6	72	>1
8	**10h**		80	506.3	65	>1
9	**10i**		92	581.6	78	>1
10	**10j**		83	473.4	63	0.75
11	**10k**		84	505.3	68	0.3
12	**10l**		81	519.5	74	0.6
13	**10m**		90[b]	545.5	45	0.3
14	**10n**		>90[b]	545.5	45	0.14
15	**10o**		84	532.3	65	0.2
16	**10p**		88	555.5	55	0.6
17	**10q**		68	516.5	59	0.2
18	**10r**		84	521.3	47	0.15
19	**10t**		83	545.5	50	0.008

- [a]The purity is calculated by the integration of the TIC trace from HPLC-MS.
- [b]By ^{1}H NMR.

As illustrated in **Table 1**, this 5-step solid phase protocol afforded products with purities greater than 80% in most cases with the exception when primary amines were used as nucleophiles (e.g., Entry 2, several other primary amines and hydrazines containing an NH_2 all gave poor purity and are not listed here). In those cases, rather complicated mixtures were obtained.[21] Yield variation from 45-84% in the table are largely due to uneven distribution of resins into individual vessels in the nucleophilic displacement step. The purity of these compounds can be exemplified by the HPLC-MS trace of product **10t** (**Figure 1**).

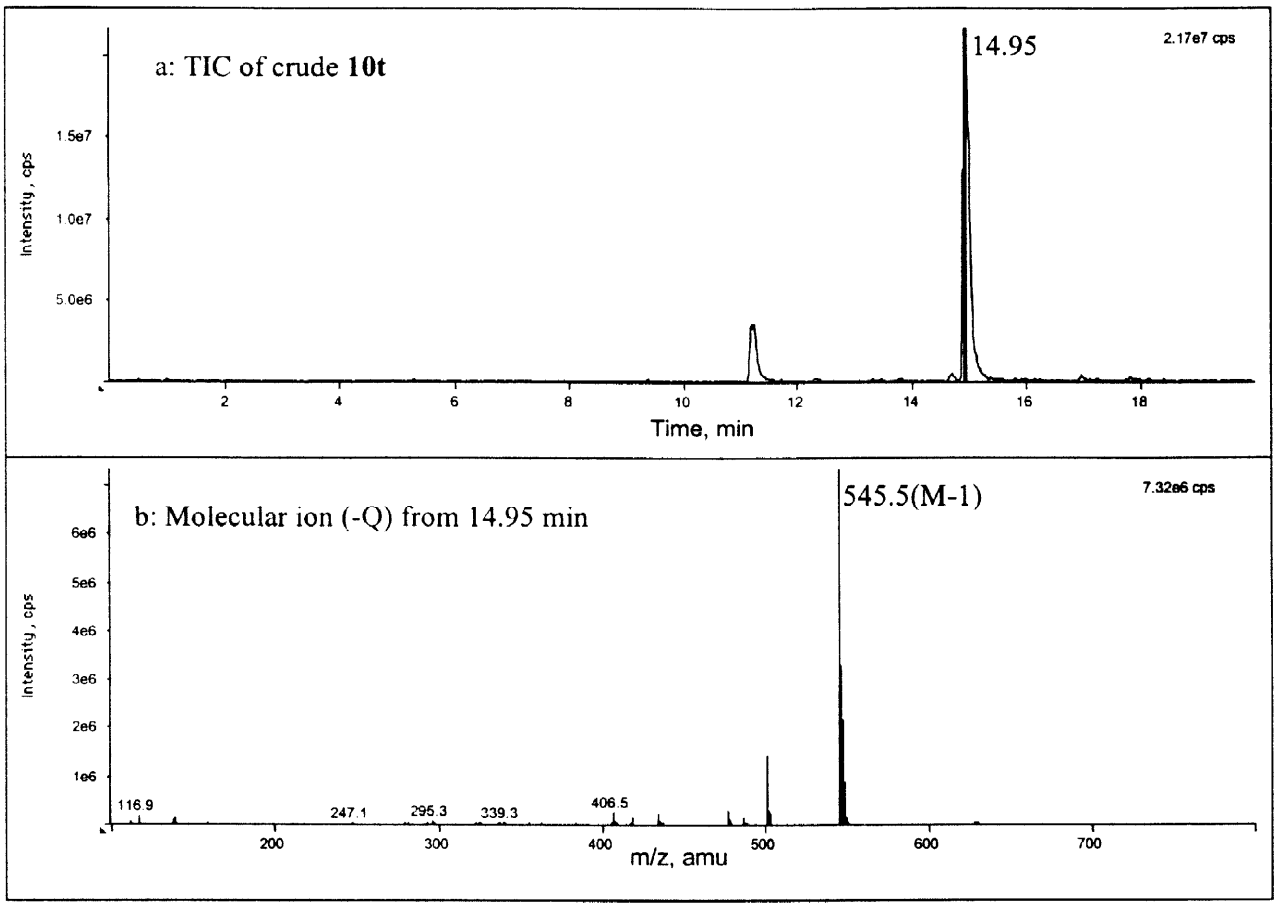
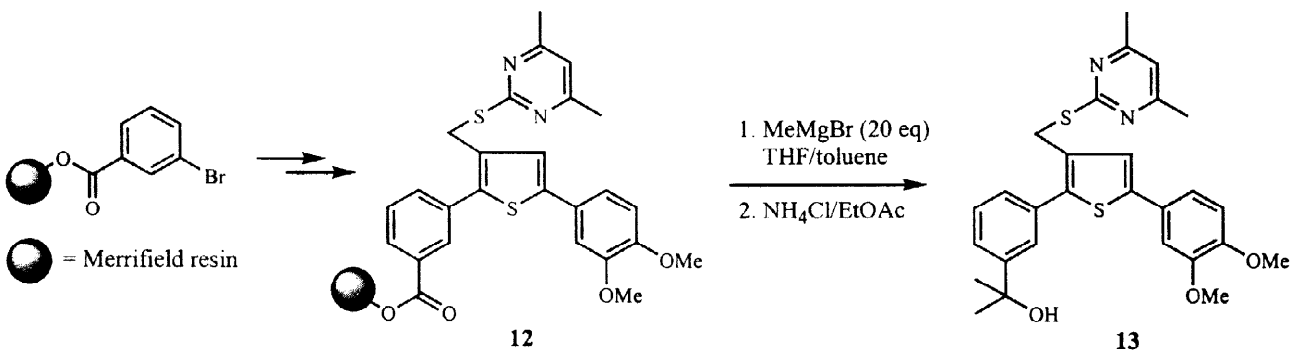


Figure 1: HPLC-MS for compound **10t**. LC conditions: 15 min 10-90% gradient using CH_3CN and 0.1%AcOH/H_2O as mobile phases and Zorbax C_{18} (4 x 50 mm) as the analytical column (1 mL/min flow rate).

The SAR of the R moiety among this class of compounds on PDE-4 is intriguing. While basic amino residues are not tolerated, substitution with sulfides generally give active compounds with IC_{50}'s in the high nM range. The most potent compound **10t** (IC_{50} 8 nM against PDE-4) incorporates a 4,6-dimethylpyrimidine-2-mercapto moiety. This compound was used as a lead for further structural modification, resulting in a series of molecules with low nanomolar potency against PDE-4. For instance, the carboxylic acid in **10t** was replaced by a dimethylcarbinol moiety, affording compounds with comparable intrinsic potencies, however, with much better whole cell activities (inhibition of TNFα production in monocytes[22]). The 3-cyclopentyloxy-4-methoxyphenyl moiety in **10t** was also substituted with a variety of aromatic or heteroaromatic residues. As an example, incorporating a 3-(4-pyridyloxy)phenyl group further improved the intrinsic potency by approximately 5 fold. A detailed SAR analysis is out of the scope of the current discussion, and instead we will focus on further chemistry development.

Other cleavage conditions: As discussed above, a dimethylcarbinol moiety served as a suitable carboxylic acid replacement. Cleavage conditions were then worked out for solid phase synthesis of these analogs as illustrated in **Scheme 3**. Among several conditions studied (MeLi, MeLi/$CeCl_3$), the use of excess

methylmagnesium bromide (MeMgBr, 20 eq, 1.4 M in toluene/THF) in THF/toluene (1:1) at room temperature furnished dimethylcarbinol analogs in moderate to good purities and yields. For example, using *m*-bromobenzoate attached to Merrifield resin, the same sequence was carried out as outlined in **Scheme 2** to afford resin **12**. Intermediate **12** was treated with MeMgBr in THF/toluene at room temperature for 2 hours and then filtered under nitrogen. The filtrate was quenched with saturated NH_4Cl (aq) and then extracted with ethyl acetate. Product **13** was obtained in greater than 85% purity (^1H NMR of the crude mixture and TLC analysis) and 62% isolated yield. The yields of the MeMgBr cleavages were generally lower than the TFA cleavages. In addition this cleavage condition does not tolerate functionalities such as ketones, esters, nitriles, etc.



Scheme 3: Cleaving with MeMgBr to give dimethylcarbinol derivatives

Other boronic acids in place of 11: The scope of the solid phase synthetic protocol was further examined with different aryl boronic acids as illustrated in **Figure 2.**[23] Most boronic acids examined worked well in the Suzuki cross-coupling reactions involving bromides such as **7** (**Scheme 2**). Boronic acids bearing a strong electron-withdrawing group such as *m*-nitrophenylboronic acid reacted with a reduced rate, and as a consequence, significant amounts (up to 25%) of debromination product **14** was observed (by HPLC/MS and ^1H NMR analysis).

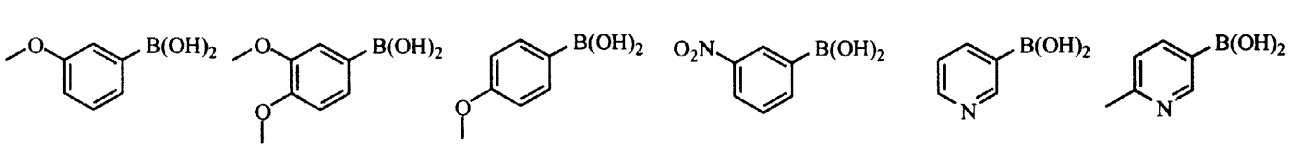
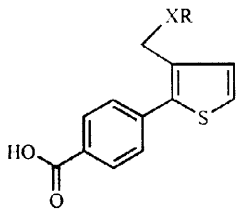


Figure 2: Boronic acids employed for solid phase thiophene synthesis



(14)

Other linkers: Our protocol also accommodates a variety of structurally diverse aryl or heteroaryl halides attached to either Wang resin or Merrifield resin. **Figure 3** summarizes some of the resins employed. When the aryl iodide is used, the reaction of boronic acid **5** can be carried out at room temperature using either $Pd(PPh_3)_4$ or Pd_2dba_3 as the catalyst. The aryl halides that did not furnish the desired product or gave complicated mixtures of products are included in the box. In the case of *o*-bromobenzoate, the first coupling reaction involving **5** was equally facile (5 eq of boronic acid was used to drive the reaction to completion). However, the second coupling reaction failed to proceed presumably due to steric hindrance. In the case of 2-chloro-5-bromobenzoate, the desired product was obtained along with several unidentified byproducts.

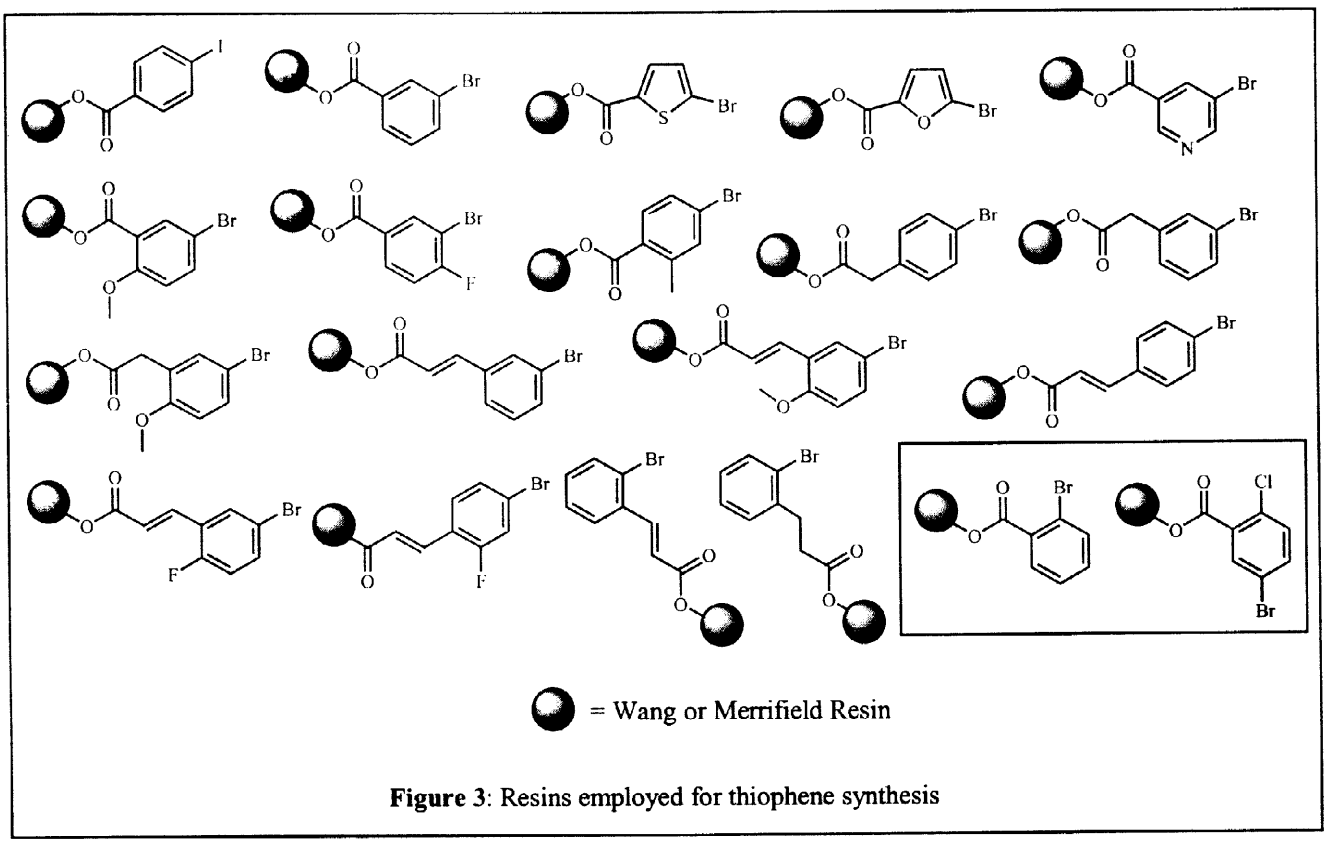


Figure 3: Resins employed for thiophene synthesis

Other nucleophiles: A variety of other thiols and secondary amines were employed for library construction (**Figure 4**). Most of them were compatible with the reaction conditions and afforded the desired

products. However, several thiols (e.g., 2-furylthiol, 6-chloro-2-mercaptothiazole, 2-mercapto-4(3H)-quinazolinone, 3-mercapto-4-methyl-1,2,4-triazole, etc.) did not give the desired products. A closer examination revealed that these thiols were either not soluble under the nucleophilic displacement conditions or the corresponding products were not stable under the cleavage conditions.

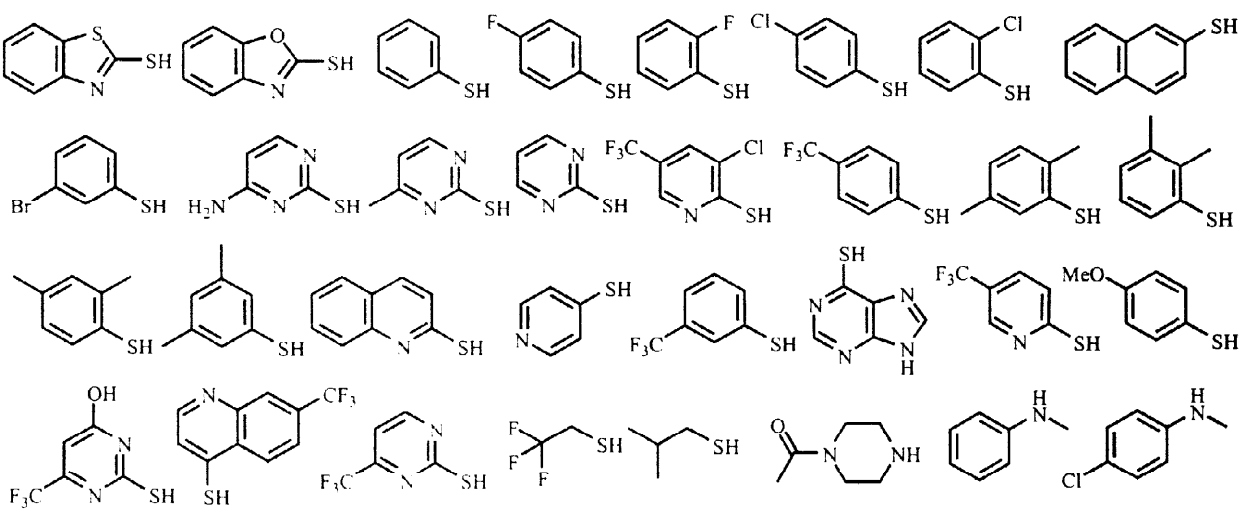
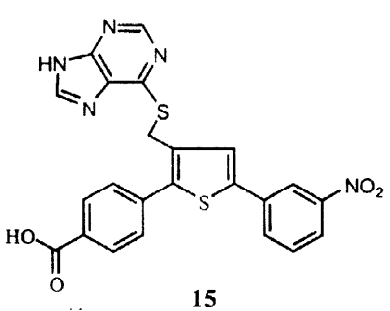


Figure 4: Other nucleophiles used for thiophene synthesis

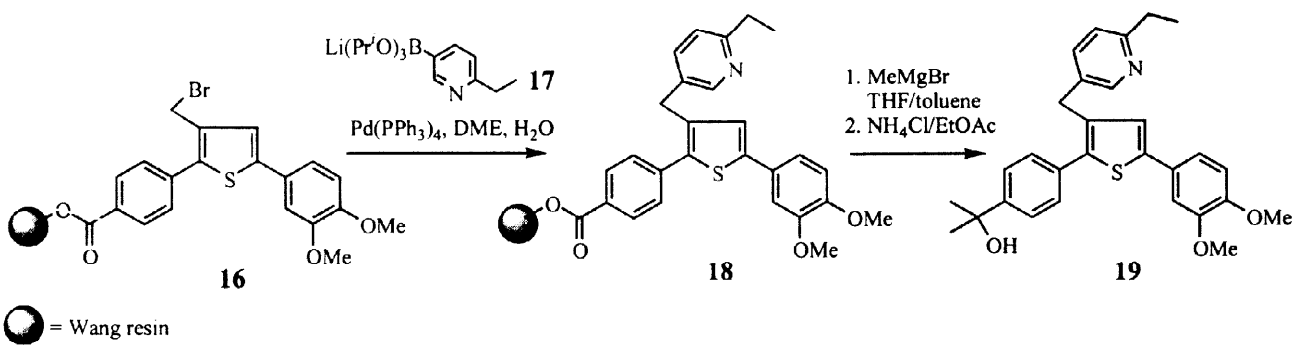
Among all the nucleophiles examined, the 4,6-dimethylpyrimidine-2-mercapto substitution was consistently superior. Interestingly, removing one methyl group (4-methylpyrimidine-2-mercapto) resulted in the loss of potency by more than 5 fold. Furthermore, abolishing both methyl groups (pyrimidine-2-mercapto) caused the loss of potency by more than 30 fold. Another interesting class of compounds were derived from the 2-mercaptopurine substitution. For example, compound **15** was active against PDE-4 with an IC_{50} of 55 nM (the activity of the corresponding 4,6-dimethylpyrimidine-2-mercapto analog was 8 nM). The purity of this compound from solid phase synthesis was shown by HPLC/MS to be 75%. The only contaminant observed was the debromination product **14** (25%) as discussed previously.



15

Purity: 75% (HPLC/MS)
m/z: 488.5 (-APCI, M-1)
IC_{50} (PDE-4): 55 nM

Borates as nucleophiles: In addition to the thiols and secondary amines, the reaction of the resin bound bromide intermediate **16** with boronic acids[24] was also briefly examined (**Scheme 4**). For instance, treating intermediate **16** with lithium borate **17**[25] (2 eq) in the presence of $Pd(PPh_3)_4$ (5%) in DME and water at 80 °C furnished the resin bound intermediate **18**. Reaction of **18** with MeMgBr gave product **19** in greater than 65% purity (judged by the ^1H NMR spectrum of the crude product) and 35% isolated yield. Interestingly, when a similar reaction was carried out in solution, a rather complicated mixture was obtained. With other boronic acids, the use of CsF as the activating agent was more advantageous.[24] The optimal conditions for this reaction are being further investigated.



Scheme 4: Borates as nucleophiles: preparation of compound **19**

In conclusion, we have demonstrated the utility of boronic acid **5** as a scaffold for solid phase parallel synthesis of structurally diverse thiophene derivatives. By using consecutive palladium catalyzed cross-coupling reaction of boronic acids (the Suzuki reaction), up to three C-C bonds can be constructed in the same sequence (e.g., **Scheme 4**). Since a large number of aryl or heteroaryl halide or triflates can be attached to solid supports, and a relatively large number of boronic acids are commercially available or can be conveniently prepared from the corresponding bromides or iodides, these powerful schemes should allow the preparation of vast amounts of compounds bearing diverse structures. The huge number of commercially available thiols and amines further enhances the capability our protocols. Due to the orthogonal nature of the approaches, these schemes can also be used for construction of mixture libraries. The discovery of a novel series of PDE-4 inhibitors with low nano-molar affinities from these thiophene derivatives serves as an example that subtle structure perturbation can have profound influence on biological activities or other properties.

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Experimental Section

General: All ^1H NMR spectra were recorded on either the Bruker 300-, 400- or 500-ARX spectrometer. Chemical ionization mass spectra were recorded on the Sciex API-100 mass spectrometer either as direct loop injection or as HPLC-MS. Melting points were recorded on the Mettler FP51 melting point apparatus and were not corrected. HPLC analysis was performed on the Waters Alliance-2690 using a photodiode array detector. HRMS were performed by the Chemistry Department at McGill University. All reagents and solvents were commercially available unless otherwise indicated. Some of the solid phase syntheses were carried out on the Merck Temperature Controlled Manual Synthesizer (the prototype of Quest-210™).

Loading of carboxylic acids to Wang resin: To a suspension of Wang resin (52.93 g, 1.2 mmol/g, Novabiochem, 200-400 mesh) in DMF (300mL) was added 4-bromobenzoic acid (38.3 g, 190 mmol), dicyclohexylcarbodiimide (DCC) (43 g, 211 mmol) and (4-N-dimethylaminopyridine) DMAP (3.9 g, 31.76 mmol) and the mixture was heated to 60 °C overnight and filtered when hot. The residual resin was washed with hot (100 °C) DMSO (5x) (to remove the dicyclohexylurea), hot MeOH (3x), THF (3x), CH_2Cl_2 (2x) and MeOH (3x). Drying under high vacuum for 2 days yielded 63 g of the loaded resin. The loading of this resin was determined to be 1.03 mmol/g by cleaving with NaOMe in THF/MeOH. When diisopropylcarbodiimide (DIC) was used as the coupling reagent, it was not necessary to washed the resin with hot DMSO as the corresponding urea formed was soluble in common organic solvents.

Determination of loading level: A suspension of resin from above (314 mg) in THF (2.4 mL) and MeOH (0.6mL) in the presence of NaOMe (15 mg) was heated to 65-70 °C under nitrogen overnight. After cooling to room temperature, the suspension was filtered and the resin was washed with THF (2x), THF/MeOH (2x) and MeOH (2x). The filtrate and washing solutions were combined and concentrated. The residue was purified by column chromatography to afford methyl 4-bromobenzoate (70 mg, 0.325 mmol) as a white solid. The loading level of this resin was calculated to be 1.03 mmol/g (0.325 mmol/0.314 g).

Loading of carboxylic acids to Merrifield resin: To a round bottom flask charged with Merrifield resin (Novabiochem, 200-400 mesh, 1-1.6 mmol/g) and DMF (250mL) was added 4-bromobenzoic acid (11.9 g, 59 mmol), Cs_2CO_3 (38.5 g, 118 mmol) and KI (3.3 g, 19.7 mmol) and the mixture was heated to 80 °C overnight. After cooling to room temperature, the mixture was diluted with 25% NH_4OAc and filtered. The residual resin was washed with DMF/H_2O (3x), H_2O (3x), DMF/H_2O (2x), DMF (2x), THF (3x) and MeOH (3x). Drying under vacuum afforded the loaded resin (28.17 g, 0.77 mmol/g).

Reaction of 5 with polymer bound (Wang resin) 4-bromobenzoate: To a suspension of the resin (6.16 g, 6.16 mmol, ~1.0 mmol/g loading) in DME (30mL) was added boronic acid **5** (1.67 g, 10.6 mmol), $Pd(PPh_3)_4$ (184 mg, 0.16 mmol) and Na_2CO_3 (2 M solution, 5.3mL) and the mixture was deoxygenated under a stream of nitrogen for 5 min under gentle stirring and then heated to 85 °C under nitrogen overnight. The mixture was filtered when hot and the resin washed sequentially with DMF (3x), DMF/H_2O (3x), DMF (2x), THF (2x) and then MeOH (3x) and dried under a nitrogen flow for 48 h to yield resin **6**.

Bromination of resin 6: resin **6** (6.2 g) was suspended in 60mL of THF and cooled to 0 °C. NBS (1.9 g, 10.6 mmol) was added followed by 1mL H_2O and the mixture was allowed to warm to rt for 1.5 h and filtered. The resin was then washed with THF (3x), DMF (3x), THF (2x) and MeOH (3x) and dried under nitrogen and then under vacuum to afford resin **7** (6.7 g).

Preparation of 3-cyclopentyloxy-4-methoxyphenylboronic acid (11): To a solution of 4-bromo-2-cyclopentyloxy-1-methoxybenzene (3.4 g, 12.5 mmol)[26] in THF (60 mL) at -78 °C was added n-BuLi (5.2 mL, 2.4M in hexanes) over 2 min and the resultant solution stirred at -78 °C for 5 min. Triisopropylborate (3mL) was added in one portion and the mixture was stirred at -78 °C for 20 min, allowed to warm to rt, and quenched with water (30mL) and acetic acid (0.75mL). Concentration in *vacuo* afforded a white solid which was filtered. The white solid was washed twice with water and dried under reduced pressure to give the desired boronic acid (2.64 g, 89% yield) as a white powder. ^{1}H NMR (400 MHz, acetone-d_6 + 1 drop D_2O): δ 7.44-7.41 (m, 2H), 6.90 (d, 1H), 4.80 (m, 1H), 3.77 (s, 3H), 1.90-1.50 (m, 8H).

Suzuki coupling of bromide 7 on solid support: A suspension of resin **7** (2.76 g), 3-cyclopentyloxy-4-methoxy-phenylboronic acid (**11**) (1.56 g, 6.6 mmol), $Pd(PPh_3)_4$ (77 mg, 0.066 mmol) and Na_2CO_3 (2 M, 3mL) in DME (27mL) was deoxygenated under a stream of nitrogen for 5 min and then heated to reflux for 7 h and poured into a 70mL fritted polypropylene tube. The solvents were flushed out with a stream of nitrogen and the resin washed sequentially with DMF (3x), DMF/H_2O (3x), DMF (2x), THF (2x) and MeOH (3x) and then dried under nitrogen overnight to afford 3.0 g of resin **8**.

Converting CH_2OH to CH_2Br: To a suspension of resin **8** (2.9 g) in dichloromethane (30mL) under N_2 at 0 °C was added Br_2PPh_3 (1.5 g, 3.48 mmol) and the mixture was stirred for 1 h and then filtered (the reaction can be carried out at room temperature as well). The residual resin was washed with CH_2Cl_2 (3x), THF (3x), ethyl acetate (2x) and ether (3x), and dried under reduced pressure to give resin **9**.

Nucleophilic displacement and cleavage: To a suspension of resin **9** (109 mg) in DMF (1mL) in a 5-mL fritted polypropylene tube equipped with a Teflon™ stopcock was added a solution of morpholine in DMF (500μL, 1M) and the mixture was shaken on an orbital shaker at 200 rpm or rotated on a disc (Glas-Col®) for 1 h. The solvent was drained and the residue washed with DMF (3x), THF (3x), MeOH (3x) and CH_2Cl_2 (3x) and the resultant resin was then treated with 1mL 20%TFA in CH_2Cl_2 (containing 5% dimethyl sulfide) for 30 min. The liquid was drained into a round bottom flask and the residual resin washed with CH_2Cl_2 (3x) and again drained into the flask. Evaporation of volatiles afforded the TFA salt of **10a** (44 mg, 84% yield) as a yellow solid. ^{1}H NMR (300 MHz, acetone-d_6): δ 8.15 (d, J = 8 Hz, 2H), 7.85 (s, 1H), 7.68 (d, J = 8 Hz, 2H), 7.27 (d, J = 2 Hz, 1H), 7.22 (dd, J = 8, 2 Hz, 1H), 7.01 (d, J = 8 Hz, 1H), 4.98 (m, 1H), 4.55 (s, 2H), 3.90 (m, 4H), 3.82 (s, 3H), 3.55-2.90 (br m, 4H), 2.00-1.60 (m, 8H). CIMS (-APCI): m/z 492.5 (M-1). HRMS (FAB$^+$) calc. for $C_{28}H_{31}NO_5S$+H$^+$: 494.2002; found: 494.2001. The procedures for making compounds **10b-10t** were similar to that of compound **10a** except that after cleavages, the desired compounds were dispensed into pre-weighed test tubes and concentrated on the Savant SC-110AR SpeedVac®.

Compound 10b: ^{1}H NMR (400 MHz, acetone-d_6): δ 8.15 (d, J = 8 Hz, 2H), 7.87 (s, 1H), 7.66 (d, J = 8 Hz, 2H), 7.26 (d, J = 2 Hz, 1H), 7.18 (dd, J = 8, 2 Hz, 1H), 6.90 (d, J = 8 Hz, 1H), 4.98 (m, 1H), 4.42 (s, 2H), 3.82 (s, 3H), 3.10 (m, 2H), 2.00-1.55 (m, 12H), 1.30 (m, 3H).

Compound 10c: ^{1}H NMR (300 MHz, acetone-d_6): δ 8.12 (d, J = 8 Hz, 2H), 7.91 (s, 1H), 7.65 (d, J = 8 Hz, 2H), 7.28 (d, J = 2 Hz, 1H), 7.21 (dd, J = 8, 2 Hz, 1H), 6.99 (d, J = 8 Hz, 1H), 4.98 (m, 1H), 4.57 (s, 2H), 3.82 (s, 3H), 3.60 (br m, 2H), 3.00 (br m, 2H), 2.00-1.55 (m, 12H). CIMS (-APCI): m/z 476.3 (M-1).

Compound 10d: ^{1}H NMR (300 MHz, acetone-d_6): δ 8.12 (d, J = 8 Hz, 2H), 7.89 (s, 1H), 7.66 (d, J = 8 Hz, 2H), 7.25 (d, J = 2 Hz, 1H), 7.20 (dd, J = 8, 2 Hz, 1H), 6.98 (d, J = 8 Hz, 1H), 4.98 (m, 1H), 4.48 (s, 2H), 3.82 (s, 3H), 3.45 (br m, 2H), 2.80 (br m, 2H), 2.00-1.55 (m, 14H). CIMS (-APCI): m/z 490.5 (M-1).

Compound 10e: ^{1}H NMR (400 MHz, acetone-d_6): δ 8.13 (d, J = 8 Hz, 2H), 7.82 (s, 1H), 7.67 (d, J = 8 Hz, 2H), 7.25 (d, J = 2 Hz, 1H), 7.22 (dd, J = 8, 2 Hz, 1H), 7.00 (d, J = 8 Hz, 1H), 4.96 (m, 1H), 4.80 (d, 12 Hz, 1H), 4.50 (d, J = 12 Hz, 1H), 3.85 (s, 3H), 3.80-3.52 (m, 3H), 2.00-1.60 (m, 12H). CIMS (-APCI): m/z 506.4 (M-1).

Compound 10f has identical ^{1}H NMR spectrum. CIMS (-APCI): m/z 506.3 (M-1).

Compound 10g: ^{1}H NMR (400 MHz, acetone-d_6): δ 8.13 (d, J = 8 Hz, 2H), 7.88 (s, 1H), 7.67 (d, J = 8 Hz, 2H), 7.25 (d, J = 2 Hz, 1H), 7.32-7.18 (m, 7H), 7.00 (d, J = 8 Hz, 1H), 4.96 (m, 1H), 4.60 (br s, 2H), 3.85

(s, 3H), 3.35 (m, 2H), 3.10 (m, 2H), 2.84 (s, 3H), 1.98 (m, 2H), 1.90-1.73 (m, 4H), 1.62 (m, 2H). CIMS (-APCI): m/z 540.6 (M-1).

Compound 10h: ^{1}H NMR (400 MHz, acetone-d_6): δ 8.14 (d, J = 8 Hz, 2H), 7.88 (s, 1H), 7.67 (d, J = 8 Hz, 2H), 7.28 (d, J = 2 Hz, 1H), 7.22 (dd, J = 8, 2 Hz, 1H), 6.99 (d, J = 8 Hz, 1H), 4.97 (m, 1H), 4.47 (s, 2H), 4.08 (br s, 1H), 3.84 (s, 3H), 3.58-2.80 (several broad multiplet, 4H), 2.20-1.60 (m, 12H). CIMS (-APCI): m/z 506.3 (M-1).

Compound 10i: ^{1}H NMR (400 MHz, acetone-d_6): δ 8.10 (d, J = 8 Hz, 2H), 7.71 (d, J = 8 Hz, 2H), 7.64 (s, 1H), 7.53 (m, 2H), 7.45-7.38 (m, 3H), 7.24 (d, J = 2 Hz, 1H), 7.22 (dd, J = 8, 2 Hz, 1H), 6.99 (d, J = 8 Hz, 1H), 4.93 (m, 1H), 4.35 (s, 2H), 4.21 (s, 2H), 3.85 (s, 3H), 3.48 (br s, 4H), 3.35 (br s, 4H), 2.00-1.75 (m, 6H), 1.63 (m, 2H). CIMS (-APCI): m/z 581.6 (M-1).

Compound 10j: ^{1}H NMR (400 MHz, acetone-d_6): δ 8.93 (s, 1H), 8.13 (d,J = 8 Hz, 2H), 7.67 (d, 2H), 7.57 (br s, 2H), 7.48 (s, 1H), 7.24-7.18 (m, 2H), 7.00 (d, J = 8 Hz, 1H), 5.70 (s, 2H), 4.89 (m, 1H), 3.85 (s, 3H), 2.00-1.75 (m, 6H), 1.63 (m, 2H). CIMS (-APCI): m/z 473.4 (M-1).

Compound 10k: ^{1}H NMR (300 MHz, acetone-d_6): δ 8.08 (d, J = 8 Hz, 2H), 7.64 (d, J = 8 Hz, 2H), 7.55-7.47 (m, 2H), 7.33 (s, 1H), 7.19-7.10 (m, 2H), 6.97 (d, J = 8 Hz, 1H), 4.90 (m, 1H), 4.60 (s, 2H), 3.82 (s, 3H), 2.00-1.55 (m, 8H). CIMS (-APCI): m/z 505.3 (M-1).

Compound 10l: ^{1}H NMR (300 MHz, acetone-d_6): δ 8.10 (d, J = 8 Hz, 2H), 7.66 (d, J = 8 Hz, 2H), 7.60 (d, J = 1.5 Hz, 1H), 7.54 (d, J = 1.5 Hz, 1H), 7.31 (s, 1H), 7.20-7.15 (m, 2H), 6.98 (d, J = 8 Hz, 1H), 4.91 (m, 1H), 4.60 (s, 2H), 3.83 (s, 3H), 3.69 (s, 3H), 2.00-1.55 (m, 8H). CIMS (-APCI): m/z 519.5 (M-1).

Compound 10m: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8 Hz, 2H), 7.60 (d, J = 8 Hz, 2H), 7.26-7.20 (m, 3H), 7.17 (s, 1H), 7.11 (dd, J = 8, 2 Hz, 1H), 7.07 (d, J = 2 Hz, 1H), 6.89-6.84 (m, 2H), 6.81 (d, J = 8 Hz, 1H), 4.83 (m, 1H), 4.12 (s, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 2.05-1.70 (m, 6H), 1.62 (m, 2H). CIMS (-APCI): m/z 545.5 (M-1).

Compound 10n: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 8 Hz, 2H), 7.55 (d, J = 8 Hz, 2H), 7.18-7.07 (m, 4H), 6.89-6.84 (m, 2H), 6.91-6.82 (m, 3H), 6.75 (m, 1H), 4.83 (m, 1H), 4.14 (s, 2H), 3.86 (s, 3H), 3.72 (s, 3H), 2.02-1.83 (m, 6H), 1.62 (m, 2H). CIMS (-APCI): m/z 545.5 (M-1).

Compound 10o: ^{1}H NMR (300 MHz, acetone-d_6): δ 8.12 (d, J = 8 Hz, 2H), 7.99 (dd, J = 8, 2 Hz, 1H), 7.76 (d, J = 8 Hz, 2H), 7.47 (s, 1H), 7.23-7.17 (m, 2H), 7.12 (m, 1H), 7.02-6.96 (m, 2H), 4.92 (m, 1H), 4.50 (s, 2H), 3.82 (s, 3H), 2.00-1.55 (m, 8H). CIMS (-APCI): m/z 532.3 (M-1).

Compound 10p: ^{1}H NMR (300 MHz, acetone-d_6): δ 8.07 (d, J = 8 Hz, 2H), 7.68 (dd, J = 8, 2H), 7.66-7.60 (m, 2H), 7.50 (s, 1H), 7.32 (m, 2H), 7.16-7.12 (m, 2H), 6.96 (d, J = 8 Hz, 1H), 4.89 (m, 1H), 4.87 (s, 2H), 3.82 (s, 3H), 2.00-1.55 (m, 8H). CIMS (-APCI): m/z 555.5 (M-1).

Compound 10q: ^{1}H NMR (400 MHz, acetone-d_6): δ 8.42 (m, 1H), 8.13 (d, J = 8 Hz, 2H), 7.74 (dd, J = 8, 2 Hz, 1H), 7.62 (m, 1H), 7.45 (s, 1H), 7.28-7.18 (m, 3H), 7.11 (m, 1H), 6.98 (d, J = 8 Hz, 1H), 4.92 (m, 1H), 4.55 (s, 2H), 3.82 (s, 3H), 2.00-1.55 (m, 8H). CIMS (-APCI): m/z 555.5 (M-1).

Compound 10r: ^{1}H NMR (400 MHz, acetone-d_6): δ 8.07 (d, J = 8 Hz, 2H), 7.55 (dd, J = 6, 1 Hz, 1H), 7.52 (d, J = 8 Hz, 2H), 7.25 (s, 1H), 7.20 (d, J = 2 Hz, 1H), 7.18 (dd, J = 8, 2 Hz, 1H), 7.08 (dd, J = 4, 1 Hz, 1H), 7.05-6.99 (m, 2H), 4.92 (m, 1H), 4.12 (s, 2H), 3.85 (s, 3H), 2.00-1.55 (m, 8H). CIMS (-APCI): m/z 521.3 (M-1).

Product 10t: A authentic sample of this compound was prepared by solution synthesis. ^{1}H NMR (300 MHz, acetone-d_6): δ 11.35 (bs, 1H, COOH), 8.14 (d, J = 8 Hz, 2H), 7.76 (d, J = 8 Hz, 2H), 7.51 (s, 1H), 7.23-7.18 (m, 2H), 6.99 (d, J = 8 Hz, 1H), 6.90 (s, 1H), 4.92 (m, 1H), 4.51 (s, 2H), 3.82 (s, 3H), 2.32 (s, 6H), 2.00-1.60 (m, 8H). CIMS (-APCI): m/z 545.5 (M-1). HRMS (FAB$^+$) calc. for $C_{30}H_{30}N_2O_4S_2$+H$^+$: 547.1726, found: 547.1725.

Preparation of Compound 13: To a suspension of resin **12** (200 mg, 1 mmol/ g,) in THF/toluene (1:1, 2mL) was added MeMgBr (3mL, 1.4M in 1:1 THF/Toluene) and the mixture was stirred at rt for 3 h. The mixture was then filtered under N_2 and the residue washed twice with toluene/MeOH (4:1). The filtrate and the washing solutions were combined, quenched with NH_4Cl (aq) and extracted with ethyl acetate (3x). The extracts were concentrated and the residue purified by preparative TLC. Eluting with 40% ethyl acetate in hexanes gave compound **13** as a white solid (63 mg, 62% yield). ^{1}H NMR: (400 MHz, acetone-d_6) δ 7.86 (s, 1H), 7.57 (m, 1H), 7.49 (s, 1H), 7.46-7.40 (m, 2H), 7.23 (d, J = 2 Hz, 1H), 7.18 (dd, J = 8, 2 Hz, 1H), 6.98 (d, J = 8 Hz, 1H), 6.89 (s, 1H), 4.46 (s, 2H), 4.18 (s, 1H, OH), 3.88 (s, 3H), 3.83 (s, 3H), 2.33 (s, 6H), 1.53 (s, 6H). HRMS (FAB$^+$) calc. for $C_{28}H_{30}N_2O_3S$+H$^+$: 507.1777; found: 507.1776. M.P.: 146.1 °C.

Preparation of Compound 19: A suspension of resin **16** (0.97 g, 0.8 mmol/g)), lithium borate **17** (487 mg, 1.62 mmol) and $Pd(PPh_3)_4$ (56 mg, 0.048 mmol) in DME (7mL) and H_2O (0.5mL) was deoxygenated under a stream of N_2 for 5 min and then heated to 80 °C for 3 h. The mixture was filtered and the residue washed with DMF (3x), DMF/H_2O (3x), THF (2x), CH_2Cl_2 (2x) and MeOH (3x) and dried under reduced pressure to yield resin **18**. To the dried resin was added MeMgBr (10mL, 1.4M in 1:1 THF/Toluene) and the mixture was stirred at rt for 5 h. The mixture was then filtered under N_2 and the residue washed twice with toluene/MeOH (4:1). The filtrate and the washing solutions were combined, quenched with NH_4Cl (aq) and extracted with ethyl acetate (3x). The extracts were concentrated and the residue purified by Flash chromatography. Eluting with 60-85% ethyl acetate in hexanes gave compound **19** as a yellow solid (128 mg, 35%). ^1H NMR: (400 MHz, acetone-d_6) δ 8.34 (d, J = 2 Hz, 1H), 7.61 (d, J = 8 Hz, 2H), 7.46-7.42 (m, 3H), 7.21-7.11 (m, 4H), 6.96 (d, J = 8 Hz, 1H), 4.08 (s, 1H, OH), 4.03 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 2.72 (q, J = 7 Hz, 2H), 1.54 (s, 6H), 1.22 (t, J = 7 Hz, 3H). HRMS (FAB$^+$) calc. for $C_{29}H_{31}NO_3S+H^+$: 474.2104; found: 474.2103.

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